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Histamine and Other Biogenic Amines in Food. From Scombroid Poisoning to Histamine Intolerance

Oriol Comas-Basté, Maria Luz Latorre-Moratalla, Sònia Sánchez-Pérez, Maria Teresa Veciana-Nogués and Maria del Carmen Vidal-Carou

Abstract

Histamine is a biogenic amine involved in important physiological activities in the organism, but its ingestion through food is associated with the onset of health disorders. Histamine intoxication, previously known as scombroid fish poisoning, is caused by the intake of foods with high levels of histamine. According to official European Union reports, more than 90% of the outbreaks registered in the last years were caused by the consumption of fish and seafood products. Histamine intolerance, on the other hand, arises when histamine degradation is impaired, mainly by a lower diamine oxidase (DAO) activity. Some of the uncertainties classically associated with histamine intoxication may be explained by this enzymatic deficit in a sensitive population. This chapter reviews the adverse effects of histamine from food within a risk analysis framework, focusing specifically on the components of risk assessment and management.

Keywords: histamine, biogenic amines, diamine oxidase (DAO), histamine intoxication, histamine intolerance, decarboxylase activity, risk assessment, risk management

1. Introduction

High amounts of biogenic amines in food are considered undesirable micro-components from the safety perspective, due to their potentially negative effects on consumer health. According to the risk assessment of biogenic amines carried out by the European Food Safety Authority (EFSA) [1], the amine content currently found in foods could be responsible of the triggering of health disorders. Histamine is the biogenic amine most commonly associated with the onset of health complaints. In fact, the triggering of symptoms derived by an excessive consumption of this amine was described for the first time over 60 years ago. It was firstly called scombroid fish poisoning, because the symptoms appeared mainly after the consumption of fish from the *Scombridae* and *Scomberesocidae* families, which have naturally high histidine contents. However, the World Health Organisation (WHO)

recommended using the term histamine poisoning or histamine intoxication, since other foods can also be involved [2]. Histamine intoxication occurs in the form of an outbreak, affecting those who have consumed a particular histamine-rich food. A few years ago, another histamine-related disorder began to be described, known as histamine intolerance, which arises from the failure of the diamine oxidase (DAO) enzyme to metabolise histamine in the intestines. This enzymatic deficit in a sensitive population may explain some of the uncertainties classically associated with histamine intoxication. In this chapter we review the available information on dietary histamine and its adverse effects, using a risk analysis approach, focusing specifically on the components of risk assessment and management.

2. Risk assessment

2.1 Hazard identification

Histamine (2-[4-imidazolyl] ethylamine) is the causative agent of both histamine intoxication and histamine intolerance. Based on its chemical structure and number of amine groups, histamine is classified as a heterocyclic diamine. Important physiological activities of histamine in the human organism include synaptic transmission, blood pressure control, allergic response and cellular growth control [1]. Histamine is also found in foods, mainly fish, fish products and fermented foodstuffs [1, 3]. The major pathway for the formation of histamine in foods is the decarboxylation of its precursor amino acid, histidine, by the action of the bacterial enzyme L-histidine decarboxylase (**Figure 1**). This enzyme requires pyridoxal-5'-phosphate (vitamin B6) as a cofactor, an exception being the pyruvoyl-dependent histidine decarboxylase of Gram-positive bacteria [3–5]. Other biogenic amines commonly found in foods are tyramine, putrescine and cadaverine and to a lesser extent β -phenylethylamine and tryptamine [3, 4, 6]. These amines are all synthesised by the microbial decarboxylation of their corresponding precursor amino acids [7]. Therefore, the accumulation of histamine and other biogenic amines in foods requires the concurrence of several factors: microorganisms with decarboxylase enzymes, the availability of precursor amino acids and favourable environmental conditions for the growth or activity of aminogenic microorganisms [6, 8].

Although the ability to decarboxylate certain amino acids is a strain-dependent property, several genera of both Gram-positive and Gram-negative bacteria associated with food spoilage and/or with technological applications can produce histamine (**Table 1**) [1, 5, 9]. *Enterobacteriaceae*, including mesophilic and psychrotolerant species of *Morganella*, *Enterobacter*, *Hafnia*, *Proteus* and *Photobacterium*, are the most prolific histamine-producing bacteria in fish [4, 7, 9, 10]. In the case of fermented foods, aside from certain strains of enterobacteria, many lactic acid bacteria are also reported as histamine-producing microorganisms [1, 9].

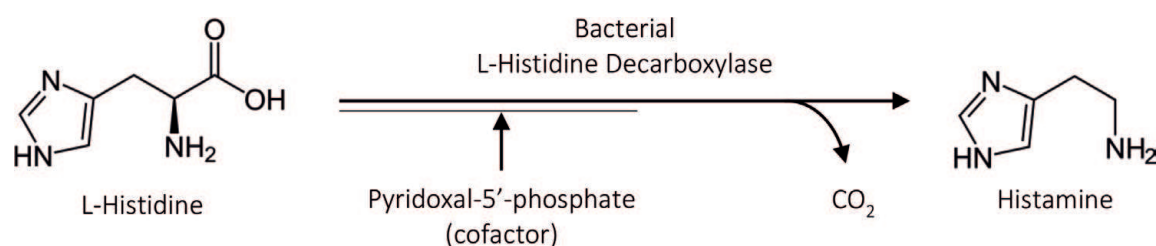


Figure 1.
Histamine formation by histidine decarboxylation.

Food	Microorganisms
Fish	<i>Morganella morganii</i> , <i>Morganella psychrotolerans</i> , <i>Klebsiella pneumonia</i> , <i>Hafnia alvei</i> , <i>Proteus vulgaris</i> , <i>Proteus mirabilis</i> , <i>Enterobacter cloacae</i> , <i>Enterobacter aerogenes</i> , <i>Serratia fonticola</i> , <i>Serratia liquefaciens</i> , <i>Citobacter freundii</i> , <i>Clostridium sp</i> , <i>Pseudomonas fluorescens</i> , <i>Pseudomonas putida</i> , <i>Aeromonas spp.</i> , <i>Pleisomonas shigelloides</i> , <i>Photobacterium phosphoreum</i> , <i>Photobacterium psychrotolerans</i>
Fermented food (cheese, dry-fermented meat sausage, wine)	<i>Lactobacillus buchneri</i> , <i>Oenococcus oeni</i> , <i>Lactobacillus hilgardii</i> , <i>Pediococcus parvulus</i> , <i>Pediococcus damnosus</i> , <i>Lactobacillus bavaricus</i> , <i>Lactobacillus brevis</i> , <i>Lactobacillus curvatus</i> , <i>Lactobacillus parabuchneri</i> , <i>Lactobacillus rossiae</i> , <i>Lactobacillus saerimneri</i> 30a, <i>E. aerogenes</i> , <i>E. cloacae</i> , <i>Escherichia coli</i> , <i>H. alvei</i> , <i>Klebsiella oxycata</i> , <i>M. morganii</i> , <i>S. liquefaciens</i> , <i>Tetragenococcus spp.</i> , <i>Leuconostoc spp.</i>

Table 1.
Histamine-producing microorganisms [1, 10].

The function of decarboxylase enzymes in bacterial metabolism is not fully understood, although it has been described as one of the primary emergency systems involved in the acid stress response [6]. Decarboxylases work in cooperation with a membrane antiporter protein, thus enabling amino acids to be transported into the cell and biogenic amines to be excreted out of the cell. Since decarboxylation consumes a proton, biogenic amine formation contributes to the regulation of intracellular pH and may also help to increase the pH of extracellular media with a low buffer capacity [5, 8]. Apart from the alkalisation effect, amino acid decarboxylation can also induce metabolic energy generation through a proton motive force, a fundamental function for bacteria without a high capacity to generate ATP [1, 5, 6, 8].

In general, food products susceptible to containing high levels of histamine are those that are microbiologically spoiled (fresh fish, meat, etc.) or fermented/cured, in which the active bacteria can present an aminogenic capacity [11, 12]. Moreover, foods rich in free histidine may be more susceptible to histamine accumulation, as is the case of scombroid fish species [7, 12]. Endogenous histamine is also found in foods that contain blood or viscera, as well as in some plant products [3, 13].

Storage temperature is one of the most important factors of histamine formation in food [7, 10, 14, 15]. High temperatures (around 25–30°C) have been described by many authors as optimal for most histaminogenic microorganisms, but significant histamine formation has also been reported in refrigerated foods (4–10°C), especially fish [14, 16, 17]. Only ice storage at near 0°C was found to retard histamine formation [17]. In fermentation processes, histamine and other biogenic amines formation is reduced at temperatures lower than 15°C [18]. Other factors, such as pH, formulation (e.g. salting, species, nitrites), starter cultures, technological conservation processes (pasteurisation, high hydrostatic pressures, irradiations) and packaging (vacuum, modified atmospheres), have been extensively studied as potential conditioners of microbial capacity to form histamine [6, 11, 12, 14].

2.2 Hazard characterisation

2.2.1 Physiological role and metabolism of histamine in the organism

Histamine is involved in vital physiological activities in the human body, including neurotransmission, immunomodulation, haematopoiesis, wound healing, circadian rhythms, regulation of cell proliferation, contraction of smooth muscle cells, vasodilatation, increased vascular permeability and mucous secretion, alterations in blood pressure, arrhythmias and the stimulation of gastric acid secretion [15, 19].

Its effects occur through the binding of histamine with four receptors (H1R, H2R, H3R and H4R) located in the target cells of various tissues. Plasma histamine levels between 0.3 and 1.0 ng/mL are considered normal [19].

In humans, two main routes of histamine metabolism are known, involving the enzymes histamine-N-methyltransferase (HNMT) and DAO (**Figure 2**). The product of HNMT-catalysed histamine methylation is N-methylhistamine (MHA), which is subsequently transformed by the monoamine oxidase (MAO) to 1-methylimidazole acetaldehyde. The latter is then converted to 1-methylimidazoleacetic acid (MIAA) by aldehyde dehydrogenase (ALDH). HNMT, a cytosolic enzyme that metabolises histamine only in the intracellular space, is expressed in almost all tissues, although mainly in the liver and kidney [15, 20]. On the other hand, the oxidative deamination of histamine by DAO leads to imidazole acetaldehyde and then, via ALDH transformation, to imidazole acetic acid (IAA), which is combined with a ribose molecule for its excretion [15, 20]. DAO, which is found mainly in the intestines, placenta and kidneys, is a secretory protein responsible for scavenging extracellular histamine after mediator release [15, 20].

2.2.2 Adverse health effects

2.2.2.1 Histamine intoxication

Histamine intoxication occurs after the ingestion of foods with unusually high amounts of histamine, which overwhelm the metabolic capacity of the organism [1, 21]. Previously known as *scombrotoxicosis*, *scombroid fish poisoning*, *pseudoallergic fish poisoning*, *histamine overdose* or *mahi-mahi flush* [1, 15], it was initially associated with ingestion of fishes from the *Scombridae* and *Scomberesocidae* families (e.g. mackerel, tuna, albacore and bonito). The first histamine intoxication was reported in sailors some centuries ago, but it was not until 1946 that publications began to describe the relationship between histamine and intoxication symptoms [9, 22, 23]. In the 1980s, the WHO recommended using the term histamine poisoning or intoxication, as the condition could be caused by the consumption of other fish species, as well as other foods [2].

The symptomatology associated with histamine intoxication is closely related to the different physiological actions of histamine in the organism. The main symptoms are neurological, gastrointestinal, dermatological and respiratory, notably rash, erythema, sweating, nausea, vomiting, diarrhoea, a sensation of burning in the mouth, swelling of tongue and face, headache, respiratory distress, palpitations and hypotension [4, 15, 21]. Symptoms are generally mild, appearing 30 minutes after ingestion and disappearing within 24 hours [4, 10, 24]. On rare occasions, they can be more severe and require medical attention [3, 4]. The severity or type of

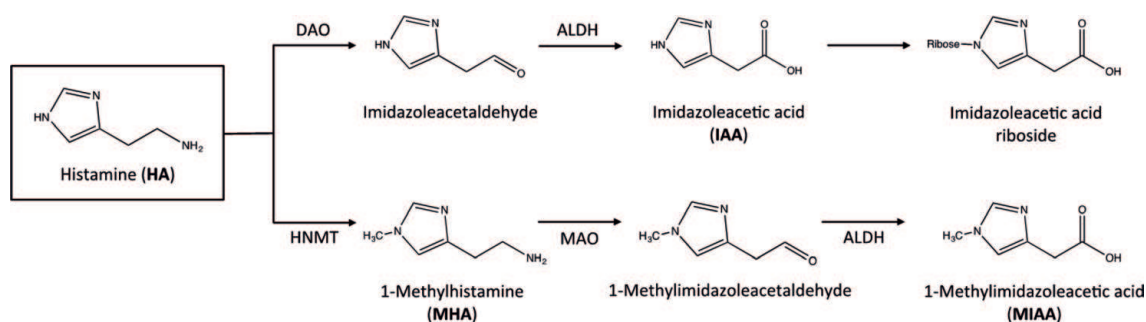


Figure 2.
Metabolic pathways of histamine in the human organism.

reaction depends on the amount of histamine in the plasma. Thus, plasma concentrations higher than the normal level of 1–2 ng/mL result in an increase in gastric secretion and heart rate; 3–5 ng/mL causes headache, flushing, urticaria, pruritus and tachycardia, 6–8 ng/mL a decrease in blood pressure, 7–12 ng/mL bronchospasm and over 100 ng/mL cardiac arrest [19].

The similarity between the described symptomatology and that of allergic reactions can lead to an incorrect diagnosis. Intoxication may be distinguished from a food allergy by taking into account the absence of an allergy history and its occurrence in an outbreak involving more than one patient over a short period of time after the consumption of foods with a high histamine load [9]. For a differential diagnosis, the concentration of serum tryptase measured within 1–2 hours of the onset of symptoms can also be helpful. In food allergy, the activity of serum tryptase increases, whereas in histamine intoxication it should remain within normal physiological values [15, 25]. Moreover, intoxication may be confirmed by elevated histamine levels in the suspected implicated food [1].

2.2.2.2 Histamine intolerance

Histamine intolerance, also known as enteral histaminosis or sensitivity to food histamine, is a disorder in histamine homeostasis mainly due to reduced intestinal degradation by a deficit of DAO activity and the resulting enhanced plasma concentrations [19, 26, 27]. This disorder is not so widely known as histamine intoxication, since the first reference regarding histaminosis or histamine intolerance dates from 1988, and most of the studies have appeared during the last 15 years [28]. DAO enzyme deficiency may have a genetic aetiology. A significant relationship has been found between lower DAO activity and the presence of different single-nucleotide polymorphisms (SNPs) in the AOC1 gene located on chromosome 7 (7q36.1) that encodes this enzyme [29, 30]. The secretion of DAO may also be inhibited by certain pathologies, especially inflammatory bowel diseases, and also by the action of drugs (acetylcysteine, clavulanic acid, metoclopramide, verapamil, etc.) [15, 19]. The role of DAO inhibitor drugs may be significant, as it has been estimated they are being consumed by approximately 20% of the European population [1, 28].

Several clinical studies have linked DAO deficiency with the appearance of gastrointestinal (abdominal pain, diarrhoea and vomiting), dermatological (atopic dermatitis, eczema or chronic urticaria) and/or neurological (headaches) complaints [31–42]. Individuals with histamine intolerance due to DAO deficiency may suffer symptoms similar to those of intoxication, but they appear after a lower histamine intake. The diagnosis is based on the presentation of at least two clinical symptoms, which go into remission when a low-histamine diet is adopted (always after ruling out positive results for food allergy) [19, 42]. Individuals with histamine intolerance can also be identified by determining serum DAO activity, although evidence for the usefulness of this analysis is still scarce and inconclusive [27, 34, 36, 43, 44]. Despite the lack of well-proven data on the incidence of histamine-intolerant individuals with a DAO deficit, it has been estimated as affecting 1% of the population [19].

2.2.3 Dose-response relationship assessment

Although a range of plasma histamine levels have been associated with the onset of different symptoms, as described above, there is no consensus on what quantities of histamine in food are responsible for intoxication outbreaks. Dose-response data from food histamine are scant [24]. According to some studies in healthy volunteers, histamine was found to trigger intoxication symptoms at levels of 75–300 mg

when administered with food (fish or non-alcoholic drinks) [1]. When histamine was administered with alcoholic beverages, levels of 0.12–4 mg in wine did not cause significant effects on healthy volunteers, whereas another trial demonstrated the onset of clinical symptoms in 12 out of 40 patients with histamine intolerance following a provocation test with 4 mg of histamine in sparkling wine [1]. Wantke et al. [45] reported the onset of symptoms after the ingestion of 50 µg of histamine in wine (125 mL) in patients with histamine intolerance. On the other hand, when 120 mg of histamine was introduced directly into the duodenum (not transported by food), symptoms appeared in patients diagnosed with chronic urticaria but not in healthy volunteers [1].

The majority of histamine poisoning outbreaks described in the literature occurred after the consumption of high amounts of histamine, mainly in fish [1]. The histamine levels in the foods associated with these outbreaks vary considerably, in the vast majority of cases with values ranging from 100 to 5000 mg/kg [46–53], although amounts of up to 10,000 mg/kg have also been reported [53].

Due to the lack of consensus to establish a threshold toxic dose for histamine intoxication, some authors have proposed some safe levels [3, 4]. Lehane and Olley [54] suggested 30 mg of histamine as a safe dose, calculated from the maximum level of 100 mg/kg of histamine in foods and based on a fish serving of 300 g and a consumer weight of 60 kg. The same authors, however, pointed out that the accuracy of their calculation was limited by an incomplete understanding of histamine intoxication. Later, Rauscher-Gabernig et al. [24] reported that dietary histamine levels in the range of 6–25 mg/meal had no adverse effects. The EFSA expert panel on biological risks proposed 50 mg/person/meal as a safe upper limit of histamine intake for healthy individuals, based on the few studies published to date [1]. This value corresponds with the 50 mg safe threshold advocated for the healthy population by the joint FAO/WHO report on health risks of histamine and other biological amines in fish and derivatives [21].

A safe level of histamine intake for intolerant individuals is not proposed in any of the studies on this disorder. The only recommendation available is from EFSA, which carried out a risk assessment of biogenic amine formation in fermented products and concluded that only foods with histamine levels below detectable limits can be considered safe for intolerant patients [1].

2.2.4 Factors contributing to histamine sensitivity

One of the most important factors affecting sensitivity to dietary histamine is the different histamine-metabolising capacity of each individual. Thus, those with a lower activity of enzymes involved in histamine metabolism (DAO, HNMT, MAO) are more sensitive to suffer the effects after histamine ingestion [1]. An impaired enzymatic activity may have a genetic explanation or be caused by intestinal pathologies or the action of drugs with an inhibitory effect [15, 19, 20]. In this context, the most studied enzyme is DAO. The enhanced sensitivity of women to histamine in certain physiological states, such as in the premenstrual period, is attributed to a reduced DAO activity [55]. Conversely, an increase in DAO production of up to 500-fold has been reported during pregnancy, accompanied by a remission of certain symptoms related to histamine intolerance [56]. Therefore, from the metabolic point of view, there is inter- as well as intra-individual variation in sensitivity.

The toxicity of histamine may be enhanced by dietary components, such as other biogenic amines or alcohol. Putrescine, cadaverine, tyramine and spermidine are biogenic amines usually found together with histamine in food and likewise are DAO substrates. Due to competition for intestinal mucin attachment sites and metabolism, the ingestion of high quantities of these other amines may

potentiate the adverse effects of histamine [1, 10, 15, 54]. This effect has been demonstrated in amines such as putrescine, cadaverine and tyramine, among others, in both in vitro and animal studies [1, 11]. These amines were found to exert an inhibitory effect on histamine metabolism when present at levels 4–5 times higher than that of histamine [11]. This potentiation mechanism could explain why symptoms do not appear when histamine is administered intravenously and yet are triggered when the same amounts of histamine are consumed in foods containing other amines [4].

Alcohol and its metabolite acetaldehyde can also have a potentiating effect. Competition for the ALDH enzyme, which is involved in the metabolism of both alcohol and histamine, results in an accumulation of histamine [1, 12]. The presence of these potentiating factors can thus explain the appearance/absence of symptoms or the variable degrees of reaction among individuals who have consumed foods containing the same amount of histamine.

2.2.5 Outbreaks of histamine intoxication in the European Union

Frequent misdiagnosis and the lack of an adequate and obligatory system for reporting histamine intoxication could account for the limited statistical data on the incidence of this food-borne disease [10, 15]. A total of 386 outbreaks were reported in 2010–2015 by different EU member states according to the EFSA reports on food-borne outbreaks [57]. In 191 of the outbreaks, the food responsible was determined with strong evidence, involving more than 1000 cases of which 107 were hospitalised (**Figure 3**). No deaths due to histamine intoxication were reported during this period. According to these data, there is no clear declining trend in the incidence of histamine intoxication in recent years, in contrast with other types of food poisoning (**Figure 3**). During this period, fish and fishery products were the primary cause of histamine intoxication in the European Union (176 outbreaks), followed by “mixed foods” (six outbreaks, three of which included a dish of tuna), “cheese” (three outbreaks), “buffet meal”, “crustaceans, shellfish, mollusc and products thereof”, “dairy products other than cheese”, “vegetables and juices and other products thereof” (one outbreak each) and “other foods” (two outbreaks) [57].

On the other hand, according to information extracted from the Rapid Alert System for Food and Feed (RASFF), there was a clear rise in notification of histamine intoxication cases linked to tuna consumption during 2014–2017, with a particularly sharp increase in 2017 [57]. In May 2017, Spain and France reported a

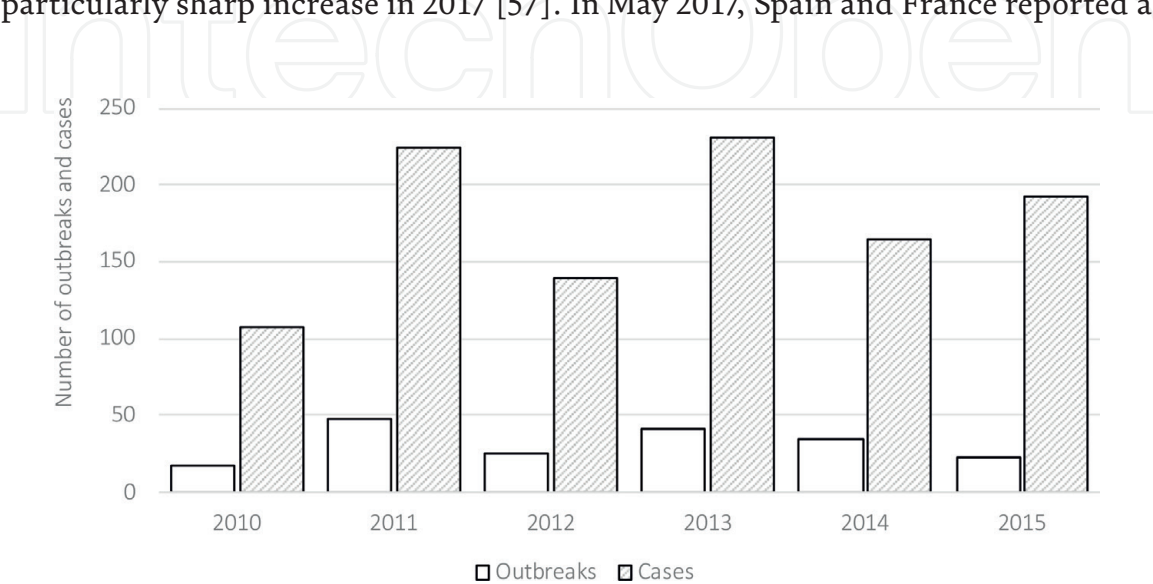


Figure 3.
Assessment of the incidence of histamine intoxication in EU countries during the 2010–2015 [57].

high incidence of histamine intoxication after the consumption of yellowfin tuna from Spain. Additional cases may have arisen in other countries that imported this food product. More than 150 people in Spain and more than 40 in France were affected after consuming tuna that was allegedly treated with a vegetable extract to alter the colour and enhance display freshness [58]. The modification of colour may mask spoilage responsible for the production of histamine and other biogenic amines.

2.3 Exposure assessment

To assess consumer exposure, it is necessary to have data on histamine levels in foods. The overall exposure to dietary histamine is difficult to estimate due to its multiple potential sources and variable concentration. **Figure 4**, which shows the distribution of histamine contents in different foods retailed in Spain, reflects this characteristic high variability, both among different food categories and within the same category.

Fresh fish and fishery products usually do not contain histamine or only low levels [59]. As shown in **Figure 4**, in most of the Spanish retail fish samples reported by Bover-Cid et al. [3], histamine was absent or found in very small quantities (P95 below 5 mg/kg). These data are in agreement with the scientific report published by EFSA based on samples of non-fermented fish and fish products from different European countries, in which only 27% of a total of 6329 samples contained histamine, usually at low concentrations (median of 2.5 mg/kg) [1]. However, a lack of freshness in raw fish and/or hygienically inadequate manufacturing processes of semi-preserved or preserved fish products can lead to markedly high histamine content. An example is the 657 mg/kg of histamine recorded within the Spanish canned fish category (**Figure 4**) or the 8910 mg/kg in fish and fishery products in the EFSA report [1]. Notably, when freshness is lost, in addition to high amounts of histamine, other amines related to the decarboxylase activity of spoilage bacteria, such as cadaverine and putrescine, also frequently accumulate.

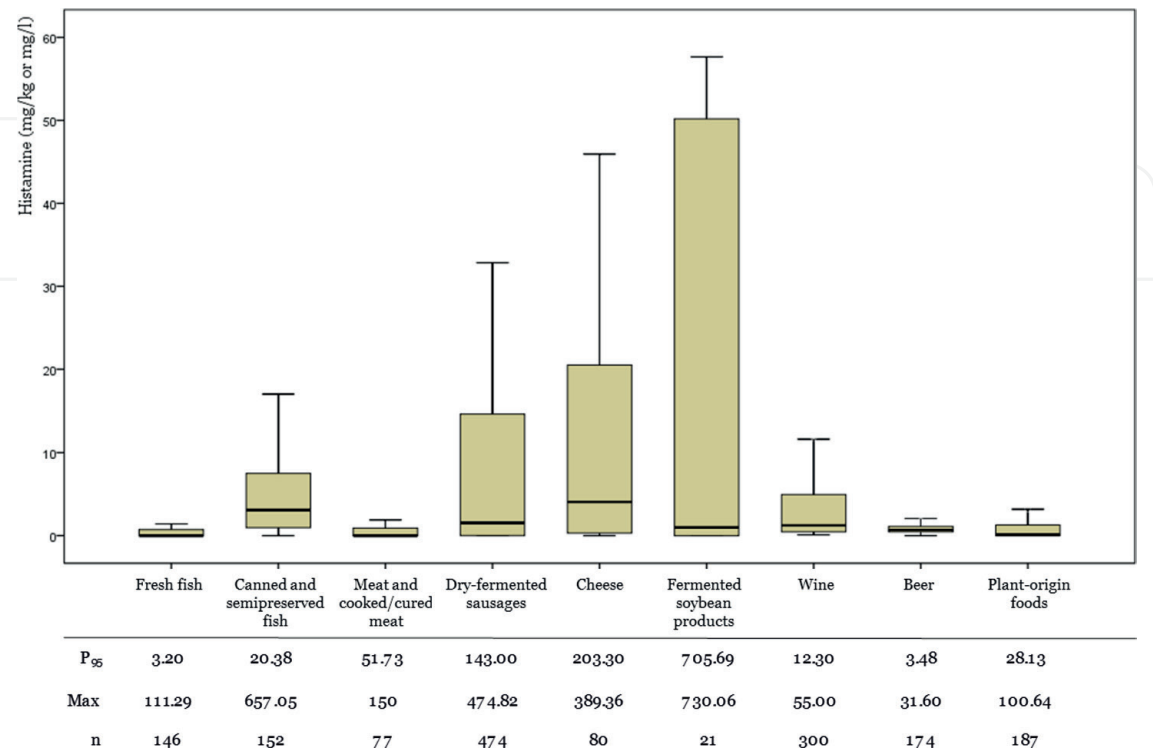


Figure 4.
Histamine distribution (mg/kg or mg/L) in different food products [3].

In fresh, cooked or cured meat, as in fish, no histamine occurrence is expected as long as freshness and a proper hygienic status of the products or manufacturing processes are ensured [1, 3, 60]. In contrast, fermented foods are susceptible to accumulating large amounts of histamine [1, 3, 5, 61]. In this type of foods, the occurrence of histamine depends not only on the hygienic conditions of the raw materials and/or manufacturing processes but also on the aminogenic capacity of the bacteria responsible for the fermentation [11, 12]. As can be seen in **Figure 4**, the presence of histamine in Spanish retail fermented foods is frequently relatively low (85% of samples below 20 mg/kg), but in some cases its levels are notably high, as in cheese (389 mg/kg), fermented sausages (475 mg/kg) or soybean products (730 mg/kg). In fermented beverages (e.g. wine and beer), histamine contents are much lower than those reported for other fermented foods. Notably, together with histamine, tyramine is usually the most frequent and abundant amine in fermented foods, because its formation is closely related to the lactic acid bacteria responsible for the fermentation processes, and its levels can reach 600 mg/kg in cheese, 700 mg/kg in fermented sausages and 1700 mg/kg in fermented vegetables. The occurrence of putrescine and cadaverine is also quite common but at lower and more variable concentrations than tyramine.

Among foods of plant origin, only some vegetables usually show significant levels of histamine, such as spinach, tomato and eggplant [13]. In these products low levels of histamine may have a physiological origin, but undesirable microbial enzymatic activity during storage can lead to the accumulation of high levels [13, 62]. Lavizzari et al. [62] reported a significant increase in histamine levels in different spinach samples stored at refrigeration temperature during 2 weeks. Histamine formation in this type of vegetables was attributed to the activity of some Gram-negative bacteria, mainly belonging to *Enterobacteriaceae* and *Pseudomonadaceae* groups, as their growth is favoured by the relatively high pH of spinach. Asparagus, pumpkin, chard and avocado rarely contain histamine and at very low levels [13]. Other types of frequently consumed foods, such as cereals, milk, yoghurt and eggs, do not show significant contents of histamine or any other biogenic amine [3].

In addition to food content, another fundamental issue when assessing exposure to histamine is the actual consumption of food by the population. Food consumption data need to be as representative as possible, with sources such as the most recent national dietary surveys.

In the exposure assessment performed by EFSA, the 95-percentiles of biogenic amine contents of different European foods and their consumption patterns were combined to provide exposure values in terms of mg/day as an estimation of a high exposure scenario [1]. For histamine, the highest exposure values were obtained for the category “fresh, frozen and canned fish” (8.8–41.4 mg/day) followed by “dry-fermented sausages” (6.4–37.1 mg/day), “cheese” (13–32.1 mg/day) and “fish sauces” (0.4–29.9 mg/day). Likewise, in an assessment of the dietary histamine exposure of Austrian consumers, it was concluded that tuna fish and some fermented products (cheese and sauerkraut) were the top contributors to the total histamine intake [24]. According to this study, a typical meal with fish as a main dish could contribute from 2.3 to 264 mg of histamine. Recently, Latorre-Moratalla et al. [63] carried out an assessment of Spanish consumer exposure to histamine derived from the consumption of dry-fermented sausages, concluding that in 95% of cases, it was lower than 6.8 mg/meal.

The larger serving size of fish products, together with the extremely high histamine contents arising from hygienic defects in their conservation or manufacturing processes, could explain why these foods contribute more to histamine exposure than others, such as cheese or dry-fermented sausages, which a priori have higher average histamine contents. This could also explain why fish and fishery products are the predominant cause of histamine intoxication.

2.4 Risk characterisation

Performing an adequate quantitative risk characterisation of histamine exposure is hampered by the lack of dose-response data. However, a qualitative approach, taking into account the limited data available, suggests that the risk of suffering histamine intoxication is relatively low, since exposure exceeds the safety limit on very few occasions.

According to the qualitative risk characterisation performed by EFSA, exposure to histamine (95-percentile value) in fermented foods does not go beyond the safe threshold of 50 mg/meal/person [1]. However, it is stressed that this upper limit may be exceeded by the consumption of more than one food item with high histamine content during the same meal. Likewise, Latorre-Moratalla et al. [63] concluded that the risk of suffering acute effects related to histamine intake after the consumption of dry-fermented sausages in Spain is very low, since the exposure levels rarely exceed the safe threshold. It should be noted that all available studies have been carried out on specific food groups and to date none have dealt with the full range of histamine-containing foods.

The risk for the histamine-intolerant population is higher, because even small amounts of histamine may trigger adverse effects [1, 63]. No studies have been carried out to evaluate this risk.

3. Risk management

From the perspective of risk management, decision-makers or the food industry should consider different actions to reduce consumer exposure to dietary histamine. For example, regulatory measures or strategies to prevent, reduce or eliminate the presence of histamine and other amines in foods could be implemented.

From a legal perspective, tolerable limits of histamine have been fixed by different countries only for fish and fishery products. The European Union through Regulation (EC) No. 2073/2005 on microbiological criteria has established that in fishery products from species with a naturally high histidine content (particularly fish from the *Scombridae*, *Clupeidae*, *Engraulidae*, *Coryphaenidae*, *Pomatomidae* and *Scomberesocidae* families), using a sampling plan of nine samples, the mean histamine value must be less than 100 mg/kg, no sample should exceed 200 mg/kg and among nine samples only two can have a histamine content between 100 and 200 mg/kg [64]. In fishery products obtained from species with a high histidine content and subjected to an enzymatic maturation treatment in brine, the maximum average value allowed is 200 mg/kg, the maximum individual value is 400 mg/kg and there can only be two samples between these two values in a sampling plan of nine samples [64, 65]. The Food and Drug Administration (FDA) of the United States, using a sampling plan of 18 samples, establishes a tolerable maximum level of 50 mg/kg of histamine for tuna and mahi-mahi or between 50 and 500 mg/kg of histamine for other fish species, with just one sample higher than these values [66]. In Canada, Switzerland and Brazil, the maximum limit allowed in fish and fishery products is 100 mg/kg and in Australia and New Zealand 200 mg/kg [7].

As histamine and other biogenic amines are a food safety concern, the food industry needs to consider improving control strategies. Available knowledge about biogenic amine formation in certain foods has made it possible to design measures to prevent or at least reduce their accumulation during manufacture and storage.

A key strategy is to guarantee and improve the hygienic quality of raw materials and manufacturing processes. Since contaminant microorganisms are responsible

for biogenic amine formation in many products, food quality and safety management based on hazard analysis and critical control points (HACCP) are essential [4, 7]. The time/temperature binomial is the most critical and determinant risk factor in biogenic amine formation in most fresh and lightly preserved meat and seafood products, as well as in raw materials (of animal and plant origin) used in the preparation of cooked, ripened or fermented products [3, 7, 11]. Predictive models of biogenic amine formation in perishable products as a function of time and temperature could be used to avoid hazardous storage conditions [11, 67]. This approach has already been implemented to reduce histamine accumulation in seafood, which is particularly associated with histamine formation by *Morganella psychrotolerans* and *M. morganii* [67]. Other factors that inhibit or reduce aminogenic activity, such as the packaging atmosphere and the addition of salt and other preservatives, should be taken into account for lightly preserved fish, meat and vegetables [6, 11].

In the case of fermented foods or beverages, the hygienic quality of raw materials may be enhanced by decreasing the microbial load through pasteurisation, a common practice in the cheese-making industry [5]. However, in fermented meat products, high temperature causes detrimental changes in the raw materials, thus rendering the conventional heat treatments unsuitable. The application of high-pressure treatments to raw materials (milk and meat) could be an effective strategy to improve their hygienic status, thereby reducing the biogenic amine accumulation without significant alteration of sensory properties [11, 68].

Techniques that avoid biogenic amine formation should also be implemented in fermented food products. For example, the use of a suitable formulation (adjusting the type and amount of fermentable sugar, spices and preservatives) and well-established technological parameters (temperature and relative humidity) enables a quick and accurate selection of desired fermentative microbiota, which limits the action of contaminant microorganisms, including amine formation [11, 18]. Moreover, it has been widely demonstrated that the selection of microorganisms without aminogenic activity for the starter cultures constitutes an effective control measure against biogenic amine accumulation in fermented products [6, 11, 18, 61]. For cases where these strategies are not sufficiently effective, a new approach currently being explored is the application of starter cultures with amino-oxidase activity, which are able to degrade previously formed amines [11, 61].

A general control strategy for wine that includes many of these approaches is the so-called low-histamine technology, which is based on the guaranteed hygienic quality of the raw materials, the addition of selected starter cultures and the use of specific production techniques that inhibit histamine formation [3]. The current challenge for the food industry is to extend this technology to other biogenic amines and other products. The successful implementation of “low biogenic amine technologies” will enable food manufacturers to produce safe and high-quality amine-free food.

4. Conclusions

Although the health problems associated with histamine consumption are well known, there are some uncertainties, especially regarding the threshold level of this amine that may trigger the symptoms. Histamine concentrations reported as responsible for intoxication outbreaks are extremely variable. Thus, despite the association of adverse effects with the ingestion of high levels of histamine, lower levels can also cause symptoms in sensitive individuals with a genetic or acquired impairment in the enzymatic degradation of histamine (the histamine-intolerant population). The difficulty in establishing a specific toxic dose is also due to the

presence of other biogenic amines in the implicated foods, which can potentiate the adverse effects of histamine.

The few qualitative risk assessments of histamine performed to date all indicate that the current risk of suffering histamine intoxication is low. However, in the population with histamine intolerance, the risk of suffering symptoms derived from the intake of histamine would be much higher. In fact, according to the risk assessment performed by EFSA, only levels below the detectable limit can be considered as safe. Therefore, for these individuals, the main strategy to avoid histamine-related health problems is to follow a diet that excludes foods rich in this or other amines, such as putrescine and cadaverine, which can potentiate the adverse effects of histamine.

According to current EU data, the consumption of spoiled fish and fishery products is the main cause of histamine intoxication outbreaks. Although this type of food usually has a low or negligible histamine content, a lack of freshness and poor hygienic conditions may result in the accumulation of high levels and trigger an outbreak. In contrast, whereas fermented foods often have higher histamine contents than fish and fish derivatives, their serving size tends to be lower, which could explain why they are generally less implicated in the outbreaks. Nevertheless, even when the risk of intoxication is low, the accumulation of high levels of histamine in fermented foods may indicate poor hygienic quality and is an argument for extending the legislative criteria to foods other than fish.

The lack of consensus on what quantities of dietary histamine produce intoxication can be explained by the coexistence of other biogenic amines in the same foods, as well as inter- and intra-individual variability in histamine metabolism. The impaired ability to metabolise ingested histamine has led to the description of a relatively new disorder, that of histamine intolerance due to DAO deficiency.

A current challenge for the food industry is to offer products with minimal biogenic amine levels, and it may be recommendable to declare the presence or absence of histamine in food labelling. Private initiatives have already begun to include the message “without histamine” in products as a hallmark of quality. Such labelling could help those with histamine intolerance to make a more informed selection of suitable foods.

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Conflict of interest

The authors declare no conflict of interest.

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